REMARKS

Reconsideration of this application is respectfully requested. Claims 310-372 and 405-453 were previously pending in this application. In place of those claims, new claims 454-575 have been added above. Accordingly, newly-submitted claims 454-575 are presented for further examination on the merits.

At the very outset, acknowledgement and appreciation is made of the courtesy extended by Examiner Scott W. Houtteman in the personal interview held on November 3, 1998 with Dr. Dean L. Engelhardt, one of the inventors and the Senior Vice President of the instant assignee, and the undersigned attorney. It is believed that the interview engendered a frank discussion of the issues remaining in the September 29, 1998 Office Action that will only serve to facilitate prosecution of this application.

Applicants and their attorneys will continue to direct all future correspondence in this application to Art Unit 1634.

A minor and obvious error in the specification has been corrected on page 53, first full paragraph. There, the designation "3′, 4′" in the context of vicinal hydroxyl groups has been changed to "2′, 3′" [vicinal hydroxyl groups]. As is well known in the art, the periodate oxidation chemistry described in that paragraph will only work with two vicinal hydroxyl groups in the *cis* orientation in the ribose sugar, e.g., the 2′, 3′ hydroxyl groups. It is quite plain, therefore, that the previous "3′, 4′" recitation was an obvious error because there is no hydroxyl group present at the 4 position. A person of ordinary skill in the art would have readily understood that only the 2′, 3′ hydroxyl groups which are vicinal and *cis* to each other could have been intended by the passage which has now been amended to correct an error which is obvious from its context.

In a sincere effort to define their invention more clearly and thereby place this application in condition for allowance, Applicants have canceled the previously pending claims in favor of new claims 454-575. In these new claims, Applicants have bifurcated the subject matter into oligo- or

polydeoxyribonucleotides (claims 454-508 and 568-571) and oligo- or polyribonucleotides (claims 511-567 and 572-575). With respect to the latter set of claims that are directed to oligo- or polyribonucleotides, Applicants have eschewed the embodiment wherein the chemical linkage for a Sig attached to a 3′ phosphate is a cleaved 3′ terminal ribose sugar previously attached to the oligo- or polyribonucleotide. Thus, each of the main independent claims, 5011, 539, 572 and 574, recite that "when Sig is attached through a chemical linkage to a terminal phosphate (PM in the case of claims 511 and 572; y in the case of claims 539 and 574) at the 3′ position of a terminal ribonucleotide, said chemical linkage is not a cleaved 3′ terminal ribonucleotide previously attached to said oligo- or polyribonucleotide [or said composition]."

The foregoing language that is now presented in Applicants' polyribonucleotide subject matter (claims 511-567 and 572-575) is well supported by their specification. In fact, on page 53, Applicants disclose in the first full paragraph:

> Broadly, in another aspect of the practices of this invention various methods are useful for the tagging or labeling of DNA in a non-disruptive manner. For example, biotin is added on the end of a DNA or RNA molecule. **The addition of biotin is accomplished by addition of a ribonucleotide. The 3′,4′**(sic)[actually, 2′,3′] **vicinal hydroxyl groups are oxidized by periodate oxidation and then reduced by a borohydride in the presence of biotin hydrazide.** Alternatively, carbodiimide can also be used to couple biotin to the aldehyde group. [bold added]

In effect, Applicants have disclosed in their own specification the periodate oxidative chemistry disclosed in Sodja cited article. The language now presented in Applicants' polyribonucleotide claims merely eschews the particular periodate chemistry already disclosed in their specification.

It is believed that the presentation of new claims 454-575 renders the instant invention unobvious and patentable over the cited prior art of record. Moreover, no new issues under 35 U.S.C. §112 are believed to be raised by these new claims. By and large, new claims 454-575 track previously pending claims apart from the bifurcation of the subject matter into

polydeoxyribonucleotde. To illustrate this point, Applicants have tracked the new claims (454-575) against previously pending claims.

New Claim No.	Previous Claim No.
454, 482, 511, 539	310, 405 (bifurcated)
455, 483, 512, 540	311
456, 484, 513, 541	312
457, 485, 514, 542	313, 314
458, 486, 515, 543	315
459, 487, 516, 544	316
460, 488, 517, 545	317
461, 489, 518, 546	318
462, 490, 519, 547	319
463, 491, 520, 548	320
464, 492, 521, 549	321
465, 493, 522, 550	322
466, 494, 523, 551	323
467, 495, 524, 552	325
468, 496, 525, 553	326
469, 497, 526, 554	328
470, 498, 527, 555	330
471, 499, 528, 556	332
472, 500, 529, 557	334
473, 501, 530, 558	302
474, 502, 531, 559	303
475, 503, 532, 560	304
476, 504, 533, 561	305
477, 505, 534, 562	306
478, 506, 535, 563	335
479, 507, 536, 564	336
480, 508, 537, 565	337
481, 509, 538, 566	309
510, 567	432
568, 570, 572, 574	433, 451-453 (bifurcated)
569, 571, 573, 575	450

Lastly, Applicants and their attorney would like to point out that a sincere effort was made to limit the number of the new claims to a number as close as possible to 122, which is the same number as was last presented by their July 6, 1998 Amendment Under 37 C.F.R. §1.115. As might be expected with bifurcation of the subject matter into roughly two divisions, either the total number of claims or the total number of independent claims would have increased significantly. In this instance, however, no additional claims are being presented, keeping the total number at 122, and the number of independent claims is no greater than the highest number of independent claims previously presented in this application, that is to say, six. In effect, there is practically no increase in the number of claims.

The Rejection Under 35 U.S.C. §112, First Paragraph

Claims 310-372 and 405-453 stand rejected for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner's remarks in that rejection are set forth on pages 2 and 3 in the September 29, 1998 Office Action.

The rejection for inadequate description is respectfully traversed.

For the sake of completeness and as a followup to their November 3, 1998 interview, Applicants would like to summarize below the principal points on the issue of adequate description all of which were set forth in their earlier filed responses.[1]

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[1] **See for example, Applicants' November 24, 1997 Amendment Under 37 C.F.R. §1.115 (page 39, through page 40, 2nd full ¶); see also Declaration of Dr. Dean L. Engelhardt In Support of Adequate Description and Enablement (page 8, indented portion bottom of page, through page 12, 1st ¶) referenced in Applicants' November 24, 1997 Amendment. See also Applicants' July 6, 1998 Amendment Under 37 C.F.R. §1.116 (footnote 1, pages 7-8).**

1. EXPLICIT DISCLOSURE OF PHOSPHATE MOIETY LABELED NUCLEIC ACIDS

Citation in the Specification	Description
page 94, last ¶, thru page 95, 1st ¶;	Still further, nucleotides in accordance with the practices of this invention include the nucleotides having the formula, **Sig** | **P — S — B . . .**
page 96, thru page 98, 1st ¶;	. . . The nucleotides are then modified in accordance with the practices of this invention by having **covalently attached thereto, to the P moiety** and/or the S moiety and/or the B moiety, **a chemical moiety Sig.**
page 103, 1st full ¶; and	The special nucleotides of this invention and polynucleotides including such nucleotides, either single-stranded or double-stranded polynucleotides, DNA and/or RNA, comprising the components, phosphoric acid moiety P, the sugar or monosaccharide moiety S, the base moiety B, a purine or pyrimidine, and the signalling or self-detecting moiety, **Sig, covalently attached to either the P, S or B moieties,** . . .
page 103, last ¶, continuing thru page 106, 1st ¶	. . . nucleotides in accordance with this invention containing the above-described components **P, S, B and Sig,** are suitably prepared . . . [bold added above]

2. OTHER EXPLICIT DISCLOSURE OF PHOSPHATE MOIETY LABELED NUCLEIC ACIDS

Citation in the Specification	Description
page 90, last ¶	. . . and a **signalling chemical moiety Sig covalently attached thereto, either to the P,** S or B **moiety.**
page 93, 1st ¶	. . . include **a chemical moiety Sig covalently attached to the P,** S and/or B moieties.
page 96, 1st ¶	. . . by having **covalently attached thereto, to the P moiety** and/or the S moiety and/or the B moiety, **a chemical moiety Sig.**

page 98, 1st ¶

. . . **the Sig component or chemical moiety of nucleotides of this invention can be directly covalently attached to the P**, S or B moieties **or attached thereto via a chemical linkage or linkage arm** . . .

page 103, 1st full ¶

. . . and **the signalling or self-detecting moiety, Sig, covalently attached to either the P**, S or B moieties, as indicated hereinabove, . . .

page 104, 1st ¶

. . . **nucleotides in accordance with this invention containing the above-described components P, S, B and Sig**, . . .

page 105, 1st ¶

. . . the nucleotides of this invention include the P, S, B and Sig components wherein the **Sig is covalently attached to either the P**, S or B moieties

page 105, 2nd ¶

The **moiety Sig attached to the special nucleotides of this invention containing the other moieties or components P**, S, B provides a site per se for the attachment thereto, the Sig component, . . .

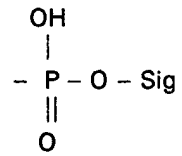
page 106, 1st ¶

. . . the special **P, S, B and Sig-containing nucleotides** of this invention, including polynucleotides containing such nucleotides . . . [bold added above]

3. EXPLICIT DISCLOSURE IN THE ORIGINALLY FILED CLAIMS

originally filed claim 143

A nucleotide having the general formula P–S–B wherein P is the phosphoric acid moiety, S the sugar or monosaccharide moiety and B the base moiety, said nucleotide having **covalently attached to the P or S or B moiety a chemical moiety Sig,** said Sig chemical moiety when attached to the P moiety is attached thereto via the chemical linkage,



and when Sig is attached to the S moiety, the S moiety is a ribose group, **said chemical moiety Sig when attached to said P**, S or B being capable of signalling itself or makes itself self-detecting or its presence known. [bold added above]

In view of the previously submitted information as summarized above, Applicants respectfully request reconsideration and withdrawal of the rejection for inadequate description under 35 U.S.C. §112, first paragraph.

The Objection and Rejection Under 35 U.S.C. §112, First Paragraph

Claims 310-372 and 405-453 stand rejected for nonenablement under 35 U.S.C. §112, first paragraph. The Examiner's remarks in the enablement rejection are given on page 3 of the Office Action.

The enablement rejection is respectfully traversed.

Again, for the sake of completeness and to follow up on the discussions held at the November 3, 1998 interview, Applicants have summarized on the next page the principal points on the enablement issue, at least a couple of which were brought to the Examiner's attention in the first instance.

Disclosure/Citation in the Specification	Comments
Example IV (page 56)	end labeling of oligodeoxyribonucleotides with terminal transferase
Example V (page 57)	provides means for labeling the oxygen or phosphorus of the phosphate moiety of a nucleotide, including the 5′ phosphate, in an oligo- or polynucleotide using procedure of Halloran and Parker, J. Immunol. 96:373 (1966)[2]
RNA ligase (page 20, 1st ¶)	phosphate labeling (attaching Sig to the 5′ phosphate)
terminal transferase (page 99, last ¶, thru page 100)	attaching Sig to the 3′ end of a nucleic acid
DNA ligase reaction (page 101, 1st ¶)	phosphate labeling (attaching Sig to the 3′ phosphate)

[2] **Applicants wish to eagerly point out that in Example V, the cited 1966 Halloran and Parker article actually discloses in Figure 1 on page 374, two separate reaction procedures for modifying the 5′ phosphate of a nucleotide (either DNA or RNA). The first reaction procedure, designated Reaction 1 in Figure 1, involves formation of a phosphodiester bond with protein seryl and threonyl residues. The second reaction procedure, designated Reaction 2, involves N-P bond formation with protein epsilon-amino groups. Figure 1 from Halloran and Parker is reproduced below:**

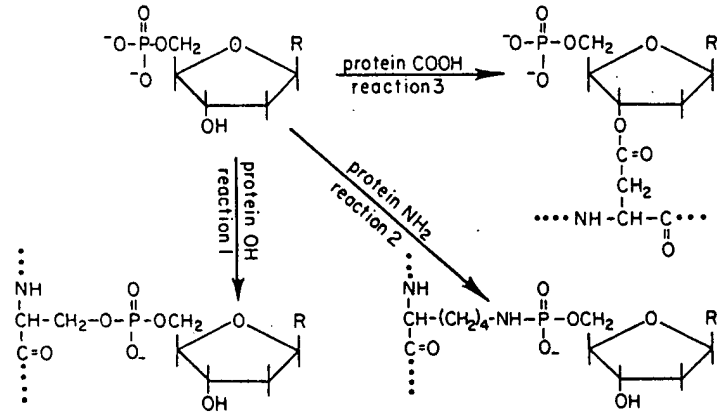


Figure 1. Possible reactions of nucleotides with proteins in the presence of carbodiimides. Very unstable products such as acyl phosphates are not shown.

In view of the foregoing information and remarks, Applicants respectfully request reconsideration and withdrawal of the enablement rejection.

The Rejection Under 35 U.S.C. §103

Claims 310-372 and 405-453 stand rejected under 35 U.S.C. §103 for being unpatentable over Gohlke et al., U.S. Patent No. 4,378,458, filed on March 30, 1981 in view of Sodja et al., Nucleic Acids Research 5(2):385-401 (1978) and further in view of Applicants' admissions. The Examiner's remarks are set forth on pages 4-6 in the Office Action.

The obviousness rejection is respectfully traversed.

As indicated in the opening remarks above, Applicants have bifurcated the subject matter of their present invention into oligo- or polydeoxyribonucleotides (claims 454-508 and 568-571) and oligo- or polyribonucleotides (claims 511-567 and 572-575). The former set of claims directed to the polydeoxynucleotides, contain similar language as was presented in the previously pending claims. The latter set of claims directed to the polyribonucleotides contain the provision that "when Sig is attached through a chemical linkage to a terminal phosphate (PM in the case of claims 511 and 572; y in the case of claims 539 and 574) at the 3′ position of a terminal ribonucleotide, said chemical linkage is not derived from a ribonucleotide previously attached to said oligo- or polyribonucleotide."

Turning to the polydeoxynucleotide claims first, claims 454-508 and 568-571, it is respectfully submitted that the cited documents, Gohlke et al. in view of Sodja et al., do not either in combination or singly, render these claims obvious for at least two very significant reasons.

First, Sodja's disclosure is limited to RNA and it does not disclose or suggest that DNA could be similarly disrupted by the periodate oxidation chemistry employed to break open the ribose sugar aldehyde ring, or by any other chemistry for that matter.

Second, Sodja's periodate chemistry can only be applied to a terminal ribonucleotide in RNA. The periodate oxidation chemistry disclosed in Sodja and Davidson requires two 2', 3' OH groups on the ribose aldehyde in the *cis* configuration. In the case of polydeoxyribonucleotides in which two hydrogens are present at the 2' position (meaning that a hydroxyl group is not present or available for oxidation), Sodja's periodate chemistry cannot be carried out. In effect, Sodja's disclosure is nonenabling with respect to *DNA* chemistry and polydeoxyribonucleotides. Thus, a person of ordinary skill in the art would have been overtly discouraged to look to Sodja's disclosure for the purpose of labeling the phosphate moiety in DNA. And Gohlke's patent, which admittedly discloses a number of labels suitable for immunoassays, would not have cured the deficiencies in Sodja's chemistry.

In the case of Applicants' polyribonucleotide claims, the cited documents do not reach the subject matter of claims 511-567 and 572-575 because no teaching or suggestion is offered for labeling nonradioactively the phosphate moiety of a polyribonucleotide directly at the 5' position or indirectly using anything other than a terminal ribonucleotide in which the ribose ring is disrupted and broken at the 2'.3' position through the periodate chemistry. Moreover, neither Sodja et al. nor Gohlke et al. teach or suggest that the phosphate moiety at any other position, such as the 2' or 3' positions, could or even should be labeled nonradioactively as set forth in the present invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection, thereby placing each of the new claims, 454-575, in allowable condition. Favorable passage to allowance is respectfully urged.

Request Under 37 C.F.R. §1.129(a) To Withdraw Finality Of Previous Office Action

Concurrently with the filing of this Amendment, Applicants are making a request under 37 C.F.R. §1.129(a) to withdraw the finality of the September 29, 1998 Office Action. Authorization for the fee in connection with Applicants' §1.129(a) Request is provided therein.

* * * * * * *

SUMMARY AND CONCLUSIONS

New claims 454-575 have been presented in place of the previously pending claims.

The total number of claims and the number of independent claims continue to be fewer than any previously presented in this application. Therefore, no claim fee or extension fee is deemed necessary in connection with the filing of this Amendment, apart from the fee for Applicants' Request Under 37 C.F.R. §1.129(a) To Withdraw The Finality of the September 29, 1998 Office Action which is being filed concurrently herewith. If any other fee is due in connection with this Amendment or Applicants' §1.129(a) request, however, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 05-1135.

If it would be helpful to expediting prosecution of this application, Applicants' undersigned attorney may be contacted during normal daytime business hours at (212) 583-0100, or by facsimile, at (212) 583-0150.

Respectfully submitted,

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